UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/714,195	11/14/2003	Joffre B. Baker	39740-0005A	5745

25213 7590 01/22/2007

HELLER EHRMAN LLP
275 MIDDLEFIELD ROAD
MENLO PARK, CA 94025-3506

EXAMINER	
SHAW, AMANDA MARIE	
ART UNIT	**PAPER NUMBER**
1634	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/22/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/714,195	BAKER ET AL.	
	Examiner	Art Unit	
	Amanda M. Shaw	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 December 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *31,35-38,40-47,51,52,56,57 and 59-61* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *31,35-38,40-47,51,52,56,57 and 59-61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12/21/2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/28/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the amendment filed December 21, 2006. Applicant's arguments have been fully considered but are not persuasive to overcome all grounds of rejection. All rejections not reiterated herein are hereby withdrawn. This action is made final.

Claims 31, 35-38, 40-47, 51-52, 56-57, and 59-61 are currently pending. Claims 31, 40-41, 51-52, 56-57, and 59-61 have been amended. Therefore Claims 31, 35-38, 40-47, 51-52, 56-57, and 59-61 will be addressed herein.

Election/Restrictions

2. In the reply filed December 21, 2006 the Applicants have once again traversed the requirement to elect a single gene or combination of genes with respect to claim 60. This claim is drawn to multiple genes. Each gene consists of a different nucleotide sequence, has a different melting temperature, a different specificity of hybridization, and encodes for a protein having a different biological activity. For example, Bak is chemically, structurally and functionally distinct from KRT17. A search for Bak would not be co-extensive with a search for KRT17. Further, a finding that Bak, for example, is novel and unobvious over the prior art would not necessarily extend to a finding that KRT17 is also novel and unobvious over the prior art. Similarly, a finding that Bak is anticipated or obvious over the prior art would not necessarily extend to a finding that KRT17 is also anticipated or obvious over the prior art. It is further noted that in the

Office Action of 12/23/2005 the Applicants were instructed to elect **one gene or a combination of genes** in Claim 60. However in the reply filed on 5/23/2006 the Applicants only elected to have CD44v6 searched. Therefore only CD44v6 has been searched with respect to Claim 60.

Information Disclosure Statement

3. The information disclosure statement (IDS) submitted on December 28, 2006 has been received. The references listed in the IDS have been reviewed as indicated on the 1449, and a copy is attached herein.

Drawings

4. The corrected drawings were received on December 21, 2006. These drawings have been accepted.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 31, 35-39, 41-47, 51-52, 56-61 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement for the reasons recited in the Office Action of June 21, 2006 and reiterated. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make

and/or use the invention. The specification does not reasonably provide enablement for methods for (i) determining the normalized level of LAMC2 or GPC3 in a sample comprising EGFR expressing cancer cells wherein an increase in LAMC2 is indicative that the patient will show a decreased likelihood of response to treatment with an EGFR inhibitor and an increase in GPC3 is indicative that the patient will show a increased likelihood of response to treatment with an EGFR inhibitor; and (ii) determining the normalized level of the corresponding gene products of LAMC2 or GPC3 in a sample comprising EGFR expressing cancer cells wherein an increase in the gene product of LAMC2 is indicative that the patient will show a decreased likelihood of response to treatment with an EGFR inhibitor and a an increase in the gene product of GPC3 is indicative that the patient will show a increased likelihood of response to treatment with an EGFR inhibitor.

The following factors have been considered in formulating this rejection (*In re Wands*, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Breadth of the Claims:

The claims are drawn broadly to methods for predicting the likelihood that a colon cancer patient will respond to treatment with an EGFR inhibitor by determining the normalized level of LAMC2, GPC3, or their corresponding gene products in a sample

comprising EGFR expressing cancer cells wherein an increase in LAMC2 or its gene product is indicative that the patient will show a decreased likelihood of response to treatment with an EGFR inhibitor and a an increase in GPC3 or its gene product is indicative that the patient will show a increased likelihood of response to treatment with and EGFR inhibitor. The term " an EGFR inhibitor" is broad in that it includes every inhibitor in the class of EGFR inhibitors. Additionally the claims encompass methods which determine the normalized level of LAMC2 and GPC3 and the corresponding gene products. The term "the corresponding gene products" is broad in that it includes every possible amino acid product which can be produced by the LAMC2 and GPC3 genes such as those that would be produced by LAMC2 and GPC3 nucleic acids having naturally and non-naturally occurring allelic, mutant, and splice variants.

Nature of the Invention

The claims are drawn broadly to methods for predicting the likelihood that a colon cancer patient will respond to treatment with an EGFR inhibitor. The invention is in a class of inventions which the CAFC has characterized as 'the unpredictable arts such as chemistry and biology" (Mycolgen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Federal Circuit 2001)).

Teachings in the Specification and State of the Art:

The specification at page 25 teaches that the EGFR is known to be active in several tumor types such as breast, colon, and head and neck cancers. The specification also teaches that several EGFR inhibitors are promising drug candidates for the treatment of EGFR expressing cancers. The specification further teaches the

following EGFR inhibitors: (i) Iressa is a small synthetic quinazoline that competitively inhibits the ATP binding site of EGFR and has been in Phase III clinical trials for the treatment of non-small-cell lung carcinoma; (ii) [agr]cyano-[bgr]methyl-N-[(trifluoromethoxy)phenyl]-propenamide (LFM-A12) has been shown to inhibit the proliferation and invasiveness of EGFR positive human breast cancer cells; (iii) Cetuximab is a monoclonal antibody that blocks the EGFR and EGFR-dependent cell growth that is currently being tested in phase III clinical trials; and (iv) Tarceva™ which has shown promising indications of anti-cancer activity in patients with advanced ovarian cancer, and non-small cell lung and head and neck carcinomas. The specification also teaches several methods of gene expression profiling such as RTPCR, microarray analysis, SAGE, mass array technology etc.

Additionally the specification does not teach that LAMC2 and GPC3 are over expressed in colon cancer. However the pre filing date art of Hlubek et al teach that the γ2 chain of laminin-5 (LAMC2) is strongly over expressed in disseminating and infiltrating tumor cells at the invasive front of colorectal carcinomas (Abstract). Filmus et al teach that GPC3 is not normally expressed in the colon however it is expressed in a significant proportion of colorectal tumors (Page21R).

Accordingly the specification is not enabled for determining the normalized level of LAMC2 or GPC3 in a sample comprising EGFR expressing cancer cells wherein an increase in LAMC2 is indicative that the patient will show a decreased likelihood of response to treatment with a EGFR inhibitor and a an increase in GPC3 is indicative that the patient will show a increased likelihood of response to treatment with a EGFR

inhibitor because the specification does not show data wherein a specific EFGR inhibitor (i.e. such as Iressa or Cetuximab) was used. The specification also does not provide an example for determining the normalized level of a representative number of corresponding gene products of LAMC2 or GPC3 in a sample comprising EGFR expressing cancer cells wherein an increase in the gene product of LAMC2 is indicative that the patient will show a decreased likelihood of response to treatment with an EGFR inhibitor and a an increase in the gene product of GPC3 is indicative that the patient will show a increased likelihood of response to treatment with an EGFR inhibitor.

The Predictability or Unpredictability of the Art and Degree of Experimentation:

The art of identifying if every EGFR inhibitor will be less effective in patients with increased LAMC2 levels or gene product levels and the art of identifying if every EGFR inhibitor will be more effective in patients with increased GPC3 levels or gene product levels is highly unpredictable.

The specification teaches following EGFR inhibitors: (i) Iressa; (ii) [agr]cyano-[bgr]methyl-N-[(trifluoromethoxy)phenyl]-propenamide (LFM-A12); (iii) Cetuximab; and (iv) Tarceva™. The specification also teaches that gene expression studies on head and neck tumors were done based on the treatment of five different EGFR inhibitor drugs. However, the specification does not teach which inhibitors are associated with the changes in the level of LAMC2 or GPC3 in head and neck cancers. The specification also teaches that gene expression studies on colon caner were done based on the treatment of an EGFR inhibitor. However, the specification does not enable practicing the invention because it does not teach which inhibitors are

associated with the changes in the level of LAMC2 or GPC3 in colon cancer. Thereby, the disclosure in the specification does not teach a representative of the broadly claimed genus of any EGFR inhibitor.

The genus of EGFR inhibitor drugs is expected to be very large. For example the post filing date art of Giaccone teach six EGFR inhibitors (Iressa, Tarceva, lapatinib, cenertinib, ZD6474, and AEE788). Giaccone additionally teaches that each of these drugs has a different mechanism in which it acts on EGFR. For example Iressa and Tarceva inhibit the tyrosine kinase of EGFR by competing with ATP for the ATP binding site, lapatinib and canertinib have activity on more members of the ErbB family, and ZD6474 and AEE788 inhibit the vascular endothelial factor receptor in addition to EGFR. Thus it is unpredictable as to whether the results obtained for colon cancer using whichever EGFR inhibitor the inventor used could be extrapolated to other EGFR inhibitors because each inhibitor works by a different mechanism.

Both LAMC2 and GPC3 are expected to be capable of producing several different gene products. The claims as written encompass all of the corresponding gene products of the LAMC2 and GPC3 genes. While the wild type LAMC2 and GPC3 nucleic acid sequences were known in the prior art, this information does not allow one to envision all possible gene LAMC2 and GPC3 gene products, including allelic, and splice mutants, as well as homologous sequences. Thus it is highly unpredictable as to whether one can determine the normalized level of a representative number of the corresponding gene products of LAMC2 or GPC3 in a sample comprising EGFR expressing cancer cells wherein an increase in any of the gene products of LAMC2 is

indicative that the patient will show a decreased likelihood of response to treatment with an EGFR inhibitor and a an increase in any of the gene products of GPC3 is indicative that the patient will show a increased likelihood of response to treatment with an EGFR inhibitor.

Amount of Direction or Guidance Provided by the Specification:

The specification teaches patients who had elevated levels of LAMC2 were less likely to respond to a treatment with an EGFR inhibitor. The specification teaches patients who had elevated levels of GPC3 were more likely to respond to a treatment with an EGFR inhibitor. However the specification does not disclose which EGFR inhibitors were used to test this hypothesis. To identify the EFGR inhibitors that were used for this study plus a representative number of the additional EFGR inhibitors would require extensive experimentation. For example, such experimentation may involve treating patients with a representative number of EFGR inhibitors and conducting multiple gene expression assays. Such random, trial by error experimentation is considered to be undue. The specification has provided only an invitation to experiment. The specification does not provide a predictable means for predicating the likelihood that a colon cancer patient will respond to treatment with any EGFR inhibitor.

Working Examples:

The specification contains two working examples. The first working example deals with gene expression studies on head and neck tumors wherein the patients were treated with five different EGFR inhibitor drugs. However, the specification does not disclose which five EGFR inhibitors were used. The second working example deals

with gene expression studies on colon caner wherein the patients were treated with an EGFR inhibitor. However, the specification does not disclose which EGFR inhibitor was used.

Conclusions:

Case law has established that '(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright* 990 F.2d 1557, 1561. *In re Fisher,* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that '(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". The amount of guidance needed to enable the invention is related to the amount of knowledge in the art as well as the predictability in the art. Furthermore, the Court in *Genetech Inc. v Novo Nordisk* 42 USPQ2d 1001 held that '(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement".

In the instant case, the claims do not bear a reasonable correlation to the scope of enablement because the specification does not teach which EGFR inhibitors were used in the working examples. The specification does not teach a representative number of EGFR inhibitors. Further the specification does not teach a representative number gene products produced by LAMC2 and GPC3. Accordingly, although the level of skill in the art of molecular biology is high, given the lack of disclosure in the specification and in the prior art and the unpredictability of the art, it would require

undue experimentation for one of skill in the art to make and use the invention as broadly claimed.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 51 remains rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for the reasons recited in the Office Action of 6/21/2006 and reiterated below.

Claim 51 remains indefinite over the recitation of the phrases: "the lysis solution". There is insufficient antecedent basis for this limitation in the claim.

Response to Amendment

7. The declaration under 37 CFR 1.132 filed on December 21, 2006 is insufficient to overcome the rejection of claims 31, 35-39, 41-47, 51-52, 56-61 based upon lack of enablement as set forth in the last Office Action.

Both the Declaration and the Applicants arguments submitted on December 21, 2006 have been fully considered but are not persuasive for the reasons set fourth below. Applicants maintain that the claimed invention is fully enabled for several reasons. The Applicants have submitted a declaration by Joffre B. Baker, PhD stating that the patients were treated with an EFGR inhibitor selected from the group: erlotinib, gefitinib, cytoximab, EMB72000, and AEE788. It is noted that on page 25 of the

specification the following EGFR inhibitors are disclosed: erlotinib and gefitinib. However the specification does not teach a method which uses these EGFR inhibitors. Further the specification does not even mention cytoximab, EMB72000, and AEE788. Further Dr. Baker states that the results presented in tables 3 and 4 were the result of treatment with these EGFR inhibitors. However the tables do not show specific data for each individual inhibitor. For example there is no data that suggests that patients with higher levels of LAMC2 have lower response rates to treatment with erlotinib. Further there is no data that suggests that patients with higher levels of GPC3 have lower response rates to treatment with erlotinib. Therefore it is still unpredictable as to whether or not the method of the present invention can be used to predict how one would respond to treatment with any EGFR inhibitor.

Additionally it is noted that the claims include detecting both LAMC2 and GPC3 RNA transcripts and their gene products. However the specification does not provide an example in which the gene products produced by LAMC2 and GPC3 are detected and used to predict the likelihood that a human colon cancer patient will respond to treatment with an EGFR inhibitor. The applicants state that since the gene products of the present invention are obtained from colon tumor tissue they must be native sequences. However they would still contain naturally occurring allelic, mutant, and splice variants. Thus both LAMC2 and GPC3 are expected to be capable of producing several different gene products. Therefore it is still unpredictable as to whether or not the gene products of LAMC2 and GPC3 can be used in the method of the present invention to predict how one would respond to treatment with any EGFR inhibitor.

Further it is noted that the Applicants have amended the claims to overcome the rejections under 35 USC 112 2nd paragraph. The amendments have been fully considered however the phrase "the lysis solution" in claim 51 still lacks antecedent because although the claim previously refers to a lysis buffer, the claim does not refer to a lysis solution.

Conclusion

8. No Claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amanda M. Shaw whose telephone number is (571) 272-8668. The examiner can normally be reached on Mon-Fri 7:30 TO 4:30. If

attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Amanda M. Shaw
Examiner
Art Unit 1634

DIANA JOHANNSEN
PRIMARY EXAMINER